REMARKS

I. Support for Amendments

The drawings were amended in order to overcome the Draftsperson's objections under 37 C.F.R. § 1.84. Claims 1 and 19 were amended to more clearly define the claimed invention. Support for these amendments is found throughout the Specification, for example, on page 4, lines 9-34, pages 21 to 24, page 28, line 15 to page 29, line 1, and Figure 9. Accordingly, no new matter is added by this Amendment and entry thereof is respectfully requested.

II. Objection to the Drawings

The Examiner objected to the drawings because they did not comply with 37 CFR § 1.84 or § 1.152. Applicants submit herewith amended drawings that comply with 37 CFR § 1.84 and § 1.152. Approval of the amended drawings is respectfully requested

III. Objection to the Information Disclosure Statement

The Examiner objected to the information disclosure statement by asserting that a listing of references in the specification is not a proper information disclosure statement. An information disclosure statement is being submitted herewith.

IV. Rejection of claims 1-9 under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-9 under 35 U.S.C. § 102(b) as allegedly being anticipated by Van Duin et al. (Biology of Reproduction, 51, 607-617, 1994)("Van Duin

reference"). The Van Duin reference is relied on in the Action for teaching the expression and purification of human zona pellucida protein ZP3 produced by Chinese hamster ovarian ("CHO") cells. This rejection is respectfully traversed for the following reasons.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). "Every element of the claimed invention must be literally present, arranged as in the claim" for an invention to be anticipated. *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989).

As stated above, the Van Duin reference teaches the expression and purification of ZP3 produced by CHO cells. However, the Van Duin reference provides no teaching of the expression and purification of ZP3 produced by *human* ovarian cells. Therefore, since Van Duin et al. does not teach every element of amended claims 1-9, the Van Duin reference does not anticipate these claims. Accordingly, withdrawal of the rejection of claims 1-9 under 35 U.S.C. § 102(b) over Van Duin et al. is respectfully requested.

V. Rejection of claim 1 under 35 U.S.C. § 102(b)

The Examiner has rejected claim 1 under 35 U.S.C. § 102(b) as allegedly being anticipated by Van Duin (WO 92/03548)("Van Duin patent"). The Van Duin patent is relied on in the Action for teaching a polypeptide and functional derivatives thereof, which have human ZP3 activity or human ZP3 antigenicity. This rejection is respectfully traversed.

The Van Duin patent teaches a polypeptide and functional derivatives thereof, which have human ZP3 activity or human ZP3 antigenicity. However, the Van Duin patent

demonstrates the expression and purification of the ZP3 protein in CHO cells and *E. coli* only. There is no teaching of how to express and purify recombinant human ZP3 in human ovarian cells.

Furthermore, the Van Duin patent fails to teach the binding assay of claim 1 whereby the complex formed between the properly glycosylated human ZP3 protein and human sperm is determined. The Van Duin patent only teaches the binding of ZP3 antibodies to human zona pellucida. These antibodies act as contraceptive agents by binding to human eggs; thereby, preventing the binding of sperm to the zona pellucida of the egg. These experiments are described on page 11 and Figure 7 and the contraceptive purpose of these ZP3 antibodies is described on page 4:

> Antibodies will be produced which recognize human ZP3 on the ovum. These antibodies will specifically bind to the sperm receptor binding site so that spermatazoa cannot bind, or otherwise the antibodies will prevent this binding through steric hindrance.

Therefore, the human sperm-zona binding assay disclosed in the Van Duin patent and cited by the Examiner measures the inhibition of sperm-zona binding caused by these ZP3 antibodies bound to the egg. By contrast, the assay of the presently claimed invention measures the binding of the glycosylated recombinant human ZP3 to the sperm itself in order to measure sperm activity, as reflected in the amended claim. Thus, while Van Duin's assay measures the binding of ZP3 antibodies to human eggs, the presently claimed invention measures the binding of the recombinant human ZP3 to sperm. The amended claims refer to this ZP3-sperm binding activity, which is not described in the Van Duin patent.

Therefore, since the Van Duin patent does not teach every element of amended claim 1, it does not anticipate this claim. Withdrawal of the rejection of claim 1 under 35 U.S.C. § 102(b) over the Van Duin patent is respectfully requested.

VI. Rejection of claims 2-8 under 35 U.S.C. § 103(a)

Claims 2-8 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Van Duin (WO 92/03548). As stated above, the Van Duin patent is relied on in the Action for teaching a polypeptide and functional derivatives thereof, which have human ZP3 activity or human ZP3 antigenicity. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the concentration of reagents to the specific concentrations in claims 2-8 in a binding assay as a means of optimizing the assay. Applicants respectfully traverse this rejection because claims 2-8, dependent on amended claim 1, are not obvious in view of the Van Duin patent for the reasons discussed below.

To properly make a rejection under 35 U.S.C. § 103, the Examiner has the initial burden of establishing a *prima facie* case of obviousness. Meeting this burden requires the Examiner to show first, that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process. Second, the Examiner must establish that the prior art would have revealed that in so making or carrying out the claimed process, those of ordinary skill in the art would have had a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the

prior art, not in Applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

As discussed above for the § 102(b) rejection, the Van Duin patent provides no teaching of the expression and purification of recombinant human ZP3 from *human* ovarian cells. Unlike the Van Duin patent disclosure, Applicants have found that only in human cell lines can the properly glycosylated ZP3 protein be produced that has both the sperm-binding activity and acrosome reaction-inducing functions of native ZP3. In contrast, the Van Duin patent does not describe that its recombinant ZP3 has any sperm binding activity at all. In fact, even Van Duin's later published reference (Van Duin et al., Biology of Reproduction, 51, 607-617, 1994 – applied by the Examiner in a separate rejection) does not establish that the CHO-expressed ZP3 has the biological activities of native ZP3. Applicants specifically address Van Duin's findings in the Specification on page 27, lines 27 to 36. There Applicants state that the Van Duin human ZP3 expressed by CHO cells displayed abnormally low acrosome reaction-inducing activity as this activity was present only at very high levels of the recombinant protein (15 to 20 μg/ml) and only after a long pre-incubation time (maximal effects observed after 18 hours). The properly glycosylated ZP3 expressed in human ovarian cells of the present invention can trigger an acrosome reaction within one hour and at a concentration of below 1 μg/ml. Therefore, the biological activity of Van Duin et al's ZP3 protein is at least 10 times lower than that of the present invention. This increased biological activity of Applicant's glycosylated ZP3 protein produced in human ovarian cells demonstrates the importance of proper glycosylation on the protein's biological abilities. Therefore, the claims have been amended to reflect that the

recombinantly produced human ZP3 of the presently claimed invention is glycosylated and expressed by human ovarian cells.

Furthermore, for the reasons set forth above, the Van Duin patent fails to teach the binding assay of claims 2-8. As discussed above, Van Duin's assay involves the use of human ZP3 antibodies. The Van Duin patent measures the amount of inhibition of sperm-zona binding caused by ZP3 antibodies bound to the egg. By contrast, the assay of the presently claimed invention measures the binding of the glycosylated recombinant ZP3 to the sperm itself. The extent of the binding between the sperm and the recombinant ZP3 provides a measurement of sperm activity. Therefore, since the Van Duin patent does not teach or suggest the binding assay of the presently claimed invention, the various concentrations of the human ZP3 protein in claims 2-8 would not have been obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully request that the rejection be withdrawn.

VII. Rejection of claim 9 under 35 U.S.C. § 103(a)

The Examiner has rejected claim 9 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Van Duin (WO 92/03548) in view of Maggio (Immunoenzyme Technique I, CRC press © 1980, pages 186-187). The Van Duin patent is relied on in the Action for teaching a polypeptide and functional derivatives thereof, which have human ZP3 activity or human ZP3 antigenicity. Maggio is relied on in the Action for teaching enzyme immunoassays, wherein either the antigen or antibody is immobilized onto a solid phase. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to

use a matrix/micro titer plate as taught by Maggio in the assay method to detect ZP3/sperm binding of Van Duin because Maggio taught that micro plates or micro titer plates "are very convenient to was thereby reducing labor in assay procedures." (Page 186, last line). Applicants respectfully traverse this rejection and submit that claim 9, dependent on amended claim 1, is not obvious in view of Van Duin and Maggio for the reasons discussed below.

For the reasons set forth above, the Van Duin patent does not teach or suggest the expression and purification of recombinant human ZP3 from human ovarian cells. Moreover, Maggio does not remedy the deficiencies of the Van Duin patent. Maggio teaches general enzyme immunoassays, wherein the antigen or antibody is immobilized onto a solid phase. There is no teaching or suggestion in Maggio to fix a glycosylated recombinant human ZP3 protein expressed from a human ovarian cell, or a sperm in the presence of glycosylated recombinant human ZP3 of the present invention, onto a matrix in order to determine human sperm activity.

Accordingly, the combination of the Van Duin patent and Maggio reference does not teach or suggest the presently claimed invention. Applicants respectfully request that this rejection of claim 9 be withdrawn.

VIII. Rejection of claim 19 under 35 U.S.C. § 103(a)

The Examiner has rejected claim 19 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Van Duin et al. (Biology of Reproduction, 51, 607-617, 1994) or Van Duin (WO 92/03548) in view of Foster et al. (U.S. Patent No. 4,444,879). As stated above, Van Duin et al. (Biology of Reproduction, 51, 607-617, 1994) is relied on in this Action for teaching the

expression and purification of human zona pellucida protein ZP3 produced by Chinese hamster ovary. Also, Van Duin (WO 92/03548) is relied on in this Action for teaching a polypeptide and functional derivatives thereof, which have human ZP3 activity or human ZP3 antigenicity. These references are further relied upon to teach the use of binding buffers and/or washing buffers in their assay techniques. Foster et al. is relied on in this Action for teaching kits including reactant reagents, a micro plate, positive controls, negative controls, standards, and instructions. The Examiner asserts that it would have been prima facie obvious to one of ordinary skill in the art at the time of Applicant's invention to take the binding/detection assay as taught by the Van Duin reference or the Van Duin patent and format them into a kit because Foster et al. teach that it is convenient to do so and one can enhance sensitivity of a method by providing reagents as a kit.

Applicants respectfully submit that Van Duin (WO 92/03548) does not teach of suggest the claimed invention for the reasons set forth above. In particular, Van Duin's assay is directed to the measurement of the contraceptive effect of ZP3 antibodies, which prevent the binding of sperm to the human zona pellucida. The assay and kit of the present invention, on the other hand, is directed to the measurement of sperm activity by observing the extent of sperm binding to properly glycosylated human recombinant ZP3, expressed from human ovarian cells. Moreover, as discussed above, the Van Duin patent teaches the use of human zona pellucida expressed and purified from CHO or *E. coli* cells. As such, the Van Duin ZP3 protein is glycosylated differently and, therefore, does not have the same biological activities of the recombinant ZP3 of the presently claimed invention. In fact, the Van Duin patent does not even discuss the ability of its ZP3 protein to bind human sperm.

Furthermore, the Van Duin reference (Biology of Reproduction, 51, 607-617, 1994) also does not teach the binding assay and kit of the presently claimed invention. First, the Van Duin reference does not demonstrate that its recombinantly-produced ZP3 protein has any binding activity with human sperm. The Van Duin reference only teaches an acrosome reaction assay in which sperm was placed with recombinant human ZP3 protein whereby the amount of sperm exhibiting dispersal of enzymes from the acrosomal region were classified as acrosome-reacted. The Van Duin reference provides no teaching of an assay to measure binding between the recombinantly produced ZP3 and sperm. In addition, the Van Duin reference only teaches the purification and expression of human ZP3 in CHO cells and does not teach its expression in human ovarian cells. Applicants reiterate that, from this disclosure, the use of human ovarian cells to express ZP3 would not have been obvious to one having ordinary skill in the art at the time the invention was made. Finally, as set forth above, the Van Duin reference does not establish that the CHO-expressed ZP3 had the full biological activities of ZP3, i.e., the sperm-binding activity and acrosome-inducing reactivity.

The Foster patent does not remedy the deficiencies of the Van Duin reference or the Van Duin patent. The Foster patent teaches an assay reagent kit comprising a microtiter plate, a supply of various immunoglobins such as IgE, buffer wash solutions, enzyme-labeled anti-Ig conjugate, enzyme specific substrate, positive and negative controls, standards and instructions. The Foster patent does not teach or suggest a diagnostic kit for sperm activity comprising compartments with glycosylated recombinant human ZP3, expressed from a human ovarian cell, and one or more reagents listed in amended claim 19.

Accordingly, Applicants assert that none of the references, taken alone or in combination, teach or suggest the presently claimed invention of claim 19. Applicants respectfully request that the rejection be withdrawn.

IX. CONCLUSION

In view of the foregoing remarks, Applicants believe that the application is in condition for allowance. However, if the Examiner disagrees, she is encouraged to call the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,

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